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THE RELATION OF TYPHUS FEVER (TABARDILLO) TO ROCKY MOUNTAIN SPOTTED FEVER*

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One who has seen Rocky Mountain spotted fever cannot fail to be impressed with certain points of similarity which the disease shows to typhus fever (typhus exanthematicus), basing the comparison on the descriptions of typhus which are given in standard treatises. These descriptions refer to typhus as it occurs in certain European and Asiatic countries. It seemed desirable, therefore, to study their relationship, along clinical, anatomical and immunological lines, at least in certain essential respects.

Our observations concern tabardillo, the typhus fever of the great Mexican plateau, which differs in some important respects from European typhus, according to the opinion of those who have studied the disease minutely (e. g., Jose Terres, in "Etiologia del Tabardillo"). It is stated that the typhus of Mexico has a more gradual onset and defervescence than that of the old world. These are both said to be very sudden in the latter, whereas in the former the fever rises gradually for three or four days during the onset, and defervescence occupies a similar period. The two diseases should again be subjected to a close comparative study in these respects.

A peculiar topographic distinction exists between the two, in that the typhus of Mexico is limited to the plateau and is said not to occur at or near sea-level; that is to say, it does not occur in the so-called "hot country" of Mexico. European typhus, on the other hand, finds its home to a large extent at sea-level. In view of the fact, however, that typhus, the world over, is a disease of temperate and cool climates, the discrepancy mentioned is only an apparent one; it loses significance when we consider that the climate of the great Mexican plateau is a temperate one, while that of the sea coast towns is warm or torrid, in which general experience indicates that typhus is not able to prevail.

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COMPARISON OF SPOTTED FEVER AND TYPHUS FEVER

Eruption.—In both spotted fever and typhus fever a macular or slightly elevated roseolar eruption occurs, which commonly becomes petechial, and which appears at about the same time in both diseases, but perhaps a little earlier in spotted fever. In typhus it is first seen at about five days after the beginning of the fever, and in spotted fever on from the second to the fifth day. In both diseases small hemorrhages (petechiæ) may occur either in the preexisting rose-colored spots or at points in the skin which were hitherto uninvolved. In the former case a petechia with a congested zone is formed, and in the latter the areola is absent. The hemorrhages appear to occur earlier and with greater regularity in tabardillo than in spotted fever, although this phenomenon is subject to great variations in the latter disease.[1] In some instances of spotted fever sharply marked petechiæ do not occur at all, while the opposite extreme occasionally is encountered, the petechiæ appearing before a roseolar eruption is definitely recognizable. Although petechiæ do not occur invariably in typhus, they would seem to be more constant than in spotted fever. In both diseases the "spots" show a certain slight degree of induration; this is quite marked in some cases of spotted fever.

There seems to be a characteristic difference in the regions of the body first involved. In spotted fever the spots first appear on the forearm and lower leg in a large percentage of the cases, whereas in typhus they are first seen on the abdomen and sides of the chest. There are variations, however, in the sequence of distribution in spotted fever, so that it is doubtful if this point is of great distinctive value.

In both infections the distribution in the end is a very general one, including the face, palms and soles: it would seem that the involvement of the palms and soles is more prominent in spotted fever than in typhus. As regards profuseness there is no essential difference.

Gangrene.—In the spotted fever of Idaho, gangrene of the foreskin and scrotum, the tonsils and faucial pillars occurs not infrequently; this is not seen so frequently in the more severe type which prevails in Montana. In typhus, the toes, feet and lower leg occasionally become gangrenous, and extensive bedsores are rather frequent.

Changes in Internal Organs.—In spotted fever the spleen is habitually enlarged. This can be determined clinically in practically all cases; and at autopsy the mass of the spleen is sometimes three or four times that of the normal organ. In Mexican typhus it shows little enlargement

1. See the Fourth Biennial Report of the State Board of Health of Montana, 1907-8, p. 137.

and this can rarely be detected clinically. In one autopsy it was of normal size; in another it was slightly enlarged, but cirrhosis of the liver was also present. In both diseases it is of rather firm consistence, in no way resembling the spleen of typhoid fever.

In spotted fever the lymph-glands are distinctly but moderately enlarged; in typhus they are smaller, but probably a little larger than normal. They show more congestion in spotted fever.

In typhus the meninges almost constantly show a great deal of congestion and edema at autopsy, so that it has sometimes been spoken of as meningeal typhus. This condition also is stated as being present in European typhus, but perhaps not as constantly as in that of Mexico. It is a minor finding in spotted fever.

At autopsy the right heart and venous system show more engorgement in spotted fever than in typhus, and this corresponds also with the clinical appearances of the two diseases.

Other organs appear uninvolved in typhus and spotted fever, except for the presence of occasional complicating infections, particularly pneumonia.

There appears to be nothing unique, therefore, as to anatomical changes, in either disease.

Fever.—In typhus the fever begins and ends with a good deal of abruptness. Two or three days may be required after onset before it reaches its high point, and an equal period is occupied in defervescence. On the other hand, the temperature in spotted fever may not reach its maximum until a week or more after onset, and defervescence may occupy a week or ten days. This is one of the marked differences between the two diseases.

Pulse.—In the early part of the course, and in mild cases throughout, the pulse in spotted fever (90-110) is slower than in typhus (110-120) under similar conditions. In both it rises to 140 or more preceding a fatal issue.

Mental Effects.—Stupefaction, or a low nervous delirium, is common to both.

Convalescence.—This varies with the severity of the infection in both diseases, but on the whole it is much slower in spotted fever than in typhus. This may be due in part to the longer duration of spotted fever.

Duration.—The "crisis" in typhus usually occurs on from the tenth to the fourteenth day, although some cases may cover a period of three weeks. Patients suffering from spotted fever are rarely convalescent until the end of the third week, and they commonly remain bedfast for from four to six weeks.

Character of the Infections.—In both, the condition is that of a systemic blood infection (and presumably lymph infection), without the critical involvement of particular organs. These points are brought out by the findings at autopsy, and by the result of inoculations with the blood of patients. Blood from spotted fever patients is always infective for the guinea-pig, monkey and certain other animals. In a number of instances reported in the literature, the blood of typhus patients apparently has produced the disease when injected into other human beings, and Nicolle's infection of the chimpanzee was done by the same means; this concerns European typhus. The experiments with Mexican typhus, reported recently by Anderson and Goldberger and by ourselves, also show that the latter is a generalized infection.

Transmission.—Spotted fever is not contagious, and the evidence indicates that the same is true of typhus. The former is transmitted by the bites of certain species of ticks, while presumably the latter is carried by the body louse (*Pediculus vestimenti*). It is probable, therefore, that they have the feature of insect transmission in common, but two altogether different types of insects are concerned.

It is a peculiar fact that the conception of contagiousness has adhered to typhus up to and including the present time. Yet, in view of the facts that typhus, when endemic in a city, remains rather strictly segregated in the poor quarters, and that more or less intimate contact is required for transmission, it is manifest that contagiousness, if present at all, must be of a peculiar character and of a low grade. Typhus has never overwhelmed a whole city as smallpox did again and again in former times. In recent years, however, belief in the theory of insect transmission of typhus has extended widely, as affording a better explanation of the epidemiologic features of the disease. Thus the flea and bedbug have repeatedly been mentioned in relation to European typhus, and Gaviño and others have called attention to the possibility of insect transmission in Mexico, without indicating the probable species, however.

The recent experiments of Nicolle in transmitting European (rather Asiatic) typhus from monkey to monkey by means of the body louse affords a good working basis for clearing up the natural means of transmission.

Our own experiments with the louse, which have been successful in a measure, will be reported at a future date.

Susceptibility of Animals.—Aside from the discrepancies between spotted fever and typhus which were mentioned above, a striking difference is found in the susceptibility of animals to the two diseases. As regards European typhus the literature contains numerous references to

attempts to infect the guinea-pig and other ordinary animals of experimentation by the injection of blood from patients, the results being uniformly negative. Likewise, in extensive experimentation with the typhus of Mexico, Director Gaviño of the Bacteriologic Institute of Mexico City, and his assistants, failed to produce any evidence of infection in guinea-pigs, rabbits, white rats and mice, by the subcutaneous and intravenous injection of blood from human patients, the blood being taken at different periods of the disease.[2] Similarly, and in substantiation of Dr. Gaviño's results, Anderson and Goldberger reported their failure to infect the guinea-pig by the injection of virulent typhus blood.[3]

These results seem so conclusive that we decided not to repeat the experiments.

In contrast to this condition, a fairly large experience has shown that spotted fever may be transmitted to the guinea-pig invariably, by the subcutaneous or intraperitoneal injection of virulent blood, provided no serious error in technic has been made.[4]

The difference in the susceptibility of the guinea-pig to the two diseases must be taken as showing definitely that typhus and spotted fever are not identical. It might also stand as sufficient reason for concluding that they could not be even related infections, were it not for the fact that there are two types of spotted fever, one of which appears to be less virulent for the guinea-pig than the other. The spotted fever of western Montana, which represents the more virulent type, can be maintained indefinitely in the guinea-pig by passage from one animal to the other. On the other hand, it has been impossible, on three occasions, by the use of the same method, to keep alive in the guinea-pig the mild type of the disease which prevails in southern Idaho. It "died out" after from two to ten passages, presumably because of a loss of virulence for the guinea-pig. Yet, other experiments, particularly that of agglutination, as performed with the bacilli found in the eggs of the tick, indicate that the two types which occur in Montana and Idaho, respectively, are identical or closely related.

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2. General reference to these experiments is made in an article by Dr. Gaviño in Gaceta Médica de Mexico, 1906, i, 218. They are also cited elsewhere in the same publication, the exact references not being before us at this moment.

3. Anderson and Goldberger: The Relation of Rocky Mountain Spotted Fever to the Typhus Fever of Mexico—A Preliminary Note, Pub. Health Rep., 1909, xxiv, 1861.

4. It is important that the blood injected should be drawn rather early in the disease, and that the quantity injected should not be too large; dilution with salt solution favors infection. This has been referred to in previous articles by one of us.

As bearing on typhus fever, this condition raises the question as to whether there may be a third type of infection (typhus fever) which is related to spotted fever, but which differs from it not only in certain important clinical respects, but also in possessing even a less degree of virulence for the guinea-pig than the mild spotted fever referred to above. In other words, may typhus fever have a group relationship to the spotted fever of the Rocky Mountains?

IMMUNIZATION EXPERIMENTS

We have resorted to protective and agglutination experiments in order to obtain more conclusive data regarding this point. The experiments may be reported briefly.

One attack of spotted fever, or of typhus, renders the individual immune to further attacks of the same disease. This acquired immunity in spotted fever is characterized by the formation of protective antibodies, which appear in the blood, and which can be demonstrated by experiments on the guinea-pig. From 0.1 to 0.2 c.c. of serum from the immune guinea-pig protects against 1.0 c.c. of virulent blood, representing from 200 to 1,000 pathogenic doses. From 0.3 to 0.5 c.c. of serum from the convalescent human patient were required to exert the same protective effect in two experiments. If typhus were identical with spotted fever, the serum from typhus convalescents should exert a similar protective effect against spotted fever; or, if typhus occupied a "group relationship" to spotted fever, this might be manifested by a certain (perhaps low) degree of protective effect against spotted fever, on the part of serum from typhus convalescents.

As will appear, the experiments to be reported do not disclose with certainty the relationship which has been suggested, and possibly they are of such value that a close relationship is actually disproved.

The immune typhus serums were all taken from patients whose course we had observed in the General Hospital (Mexico City), and in whom the diagnosis of typhus seemed to be without doubt. Their histories will not be recited. The blood was drawn on from the seventh to the tenth day after the subsidence of fever, after the patients had left their beds, and the serum obtained by defibrination and centrifugation, or by spontaneous clotting.

Three sets of controls were utilized: first, the protective power of normal human serum as compared with that from the typhus convalescents; second, the tests of the toxicity of human serum alone for the guinea-pig; third, inoculations to determine approximately the strength (quantity or virulence) of the spotted fever virus used in each experi-

THE PROTECTIVE POWER OF CONVALESCENT TYPHUS SERUM AGAINST SPOTTED FEVER

	Immune typhus serum, c.c.	Normal human serum, c.c.	Spotted fever virus, c.c.	Guinea-pig.	Incubation period, days.	Duration of fever, days.	Result. Remarks.
EXPERIMENT 1							
Case 2, R.	2.0	...	1.0	2644	3	9	Death. Autopsy: spotted fever.
	1.0	...	1.0	2645	3	13	Death. Autopsy: spotted fever.
	0.5	...	1.0	2646	3	14	Death. Autopsy: spotted fever.
Controls	...	2.0	1.0	2647	3	6	Death. Autopsy: spotted fever.
	...	1.0	1.0	2648	3	11	Recovery.
	...	0.5	1.0	2649	3	8	Death. Autopsy: spotted fever.
Controls with virus	...	...	0.1	2650	4	.....	Killed on sixth day of fever.
	...	...	0.05	2651	3	.....	Killed on sixth day of fever.
	...	...	0.01	2652	4	8	Death. Autopsy: spotted fever.
To determine toxicity of serum	...	2.0	.....	2653	...	.....	
	...	1.0	.....	2654	...	.....	
	...	0.5	.....	2655	...	.....	No fever. Remained well.
	2.0	...	.....	....	...	.....	
EXPERIMENT 2							
Case 1. M—a	3.0	...	0.5	2669	5	9	Recovery.
	2.0	...	0.5	2670	4	10	Recovery.
Controls	...	3.0	3.0	2671	4	8	Death. Autopsy: spotted fever.
	...	2.0	0.5	2672	2-3	14-15	Death. Autopsy: spotted fever.
Controls with virus	...	...	0.1	2673	3	.....	Killed on 7th day.
	...	...	0.05	2674	4	10	Recovery.
	...	...	0.01	2675	6	7	Death. Autopsy: spotted fever.
To test toxicity of serum	3.0	...	.....	2676	...	.....	Accidental death.
	2.0	...	.....	2677	...	.....	Not sick.
EXPERIMENT 3							
Case 17. P—a	3.0	...	0.1	1 x	4	6	Death. Autopsy: spotted fever.
	2.0	...	0.1	2 x	6	6	Recovery.
	1.0	...	0.1	3 x	5-6	7-8	Death. Autopsy: spotted fever.
Control	...	3.0	0.1	4 x	4	7	Death. Autopsy: spotted fever.
Control with virus	...	...	0.005	5 x	4	7	Death. Autopsy: spotted fever.
EXPERIMENT 4							
Case 24. E—a	2.0	...	0.01	9 x	...	.....	Slight rise in temperature, but sufficient to vaccinate; immune to immunity test given 2 weeks later.
	1.0	...	0.01	10 x	...	.....	No fever. Protection complete, but not accompanied by vaccination; became infected in immunity test 2 weeks later.
Controls	...	2.0	0.01	8 x	6	6	Death. Autopsy: spotted fever.
	...	1.0	0.01	11 x	...	.....	Slight fever, resulting in vaccination as shown by immunity test given 2 weeks later.
Control with virus	...	...	0.005	12 x	...	.....	Slight fever, resulting in vaccination, resulting as shown by immunity test given 2 weeks later.

ment. The virus was that represented in the defibrinated blood of the infected guinea-pig on the third day of its fever.

The virus and serums were mixed, and injected intraperitoneally as soon as possible thereafter; the syringe was washed with salt solution and the washings injected, in order to render the experiments as nearly quantitative as possible.

It will be noted that, as the experiments progressed, the proportion of convalescent typhus serum to spotted fever virus increased from ½ to 1 (Experiment 1), to 200 to 1 (Experiment 4).

One would expect to find evidence of a protective power in absolute prevention of infection, or, if present to a low degree, in a prolongation of the incubation period above that of the controls, in a shorter course of fever, or in recovery as compared with the death of the controls. Three animals in the series, 9a, 11a and 12a, suffered such light attacks that they could not be recognized positively by the temperatures exhibited, the result being determined only by immunity tests which were administered later. The accompanying table gives the outlines of the experiments.

Analysis of the table shows with reasonable clearness that the typhus serum exerts no more protective effect than does normal serum. Interest centers chiefly in Experiment 4, in which the dose of virus was approximately twice the minimum infective quantity. The immune typhus serum showed a certain degree of protection in doses of 1.0 and 2.0 c.c., but on the other hand, 1.0 c.c. of normal serum showed the same degree of protective power. We may consider that the dose of virus used was so low that very slight influences were able to determine the occurrence or non-occurrence of infection.

Another experiment also indicates that an attack of typhus fever in the monkey does not protect the animal against a subsequent infection of spotted fever virus. Monkey 11 was inoculated with typhus by means of blood drawn from Monkey 7 on the eighth day of the latter's fever. After an incubation period of nine or ten days the temperature of No. 11 rose, and the animal passed through a course of fever similar to that which has appeared in other animals inoculated with virulent typhus blood. Twenty-seven days after the inoculation and after recovery was complete a second injection of typhus virus, consisting of 5 c.c. of blood from a human patient, was given to No. 11, in order to determine immunity or non-immunity to the disease. No fever resulted over a period of eighteen days. A control monkey (No. 21) which received a similar injection passed through a course of fever resembling that of typhus. We may, therefore, consider that No. 11 had been infected by its first injection of typhus virus, and that this resulted in immunity to the disease.

In order to test the animal's immunity to spotted fever, after the lapse of some days it was injected intraperitoneally with 3 c.c. of defibrinated blood from the infected guinea-pig, drawn on the third day of the latter's fever. The blood was diluted to 6 c.c. by means of salt solution before being injected. The following course of fever developed:

	A. M.	P. M.
March 13	102	102.4
March 14	102.6	103.3
March 15	102	102.4
March 16	103	104.6
March 17	104.7	105.6
March 18	103.1	106.4
March 19	104.6	106.7
March 20	104	105.6
March 21	105.8	106.8
March 22	105	106.6
March 23	101.4	104.1
March 24	99	103

On March 23 and 24 an extensive hemorrhagic eruption developed on the extremities, tail and back, such as has occurred previously in spotted fever in the monkey.

As a control a guinea-pig inoculated with 1 c.c. of the same virus developed a typical course of spotted fever, as did a second guinea-pig inoculated with the blood of No. 11.

This experiment indicates, therefore, that an attack of typhus in the monkey does not render him immune to spotted fever, although it does protect him against infection from a second injection of virulent typhus virus.

AGGLUTINATION EXPERIMENTS

As reported previously by one of us, immune spotted fever serum agglutinates to a marked degree a bacillus which occurs in the eggs of ticks which act as carriers of the disease. The agglutination is specific, in that normal serums do not have this agglutinating effect, or have it to a very low degree; and this, among other reasons, is taken to indicate that the organism bears a causal relation to spotted fever.

This reaction was utilized as a means of determining a possible relation between spotted and typhus fevers. As in previous experiments, an emulsion of the bacilli was obtained by crushing a sufficient number of eggs in a small quantity of salt solution, and with this emulsion the microscopic agglutination test was performed with various dilutions of serum from convalescent typhus patients. Duplicate preparations with normal human serum were made, and, in addition, with immune spotted fever serum from the guinea-pig in order to make certain of the character of the bacilli.

In the case of the immune spotted fever serum the agglutination was marked or complete in three experiments up to a dilution of 1 in 500. Numerous experiments have shown that serum from normal guinea-pigs agglutinates only in dilutions of 1-10 to 1-20. Normal human serum caused slight agglutination at low dilutions (1 in 10 and 1 in 20). The serum of typhus convalescents, drawn within a week to ten days after the subsidence of fever, had approximately the same agglutinating power as the normal serum in two experiments, while in a third it reached a dilution of 1 in 40. Even in this case, however, the agglutination was not complete at this dilution.

SUMMARY AND CONCLUSIONS

The serum of typhus convalescents, drawn within a week to ten days after the subsidence of fever, exerts no more protective effect against spotted fever than normal serum does.

Also, such serums show little or no more agglutinating effect for the bacilli which appear to be associated with spotted fever than do normal serums.

A monkey which had been rendered immune to typhus was not immune to spotted fever.

These experiments go to substantiate the clinical evidence and that obtained by animal inoculations, that spotted fever and typhus fever are not identical, and they seem also to indicate that the organisms of the two diseases are not closely related biologically, whatever the morphologic conditions may be.

The fact also that the serum of a disease (typhus) which is roughly similar to spotted fever, has no unusual agglutinating power for the bacilli mentioned, as compared with the high agglutinating power of immune spotted fever serum, supports the contention that this bacillus bears a causal relation to spotted fever.

We are indebted to Director Gaviño of the Bacteriologic Institute and to his assistant, Dr. Girard, for the use of their laboratory and for numerous courtesies, to Dr. Escalona of the General Hospital for his cooperation and to Mr. J. J. Moore of the University of Chicago for assistance in the experiments.